Remarks

The present communication is responsive to the Official Action of April 16, 2010, in the nature of a restriction requirement. Claims 62-79 presently appear in this case. All of the claims have been subject to a unity of invention restriction requirement.

Briefly, the present invention relates to a method of administering a medicament to the GI mucosa of a subject having a disease or disorder associated with inflammation of the GI mucosa. The medicament is administered in a manner and amount effective to achieve topical treatment of the GI mucosa. The medicament comprises negatively charged lipid assemblies loaded with an active ingredient. The active ingredient is not covalently bound with the lipid assemblies.

Claim 62 has been amended to place it better form for further examination. The route of treatment has been specified as being "in a manner and amount effective to achieve topical treatment of said GI mucosa" and the active ingredient was specified as one that is "effective for the topical treatment of said GI mucosa." Support for these amendments is found on page 8, lines 18-19, of the specification, where it states, "… lipid assemblies loaded with an active ingredient, the amount being effective to

achieve topical treatment of said GI mucosa." See also the following paragraph. Further support is found on page 14 of the description, where it states:

> The successful targeting is preferably used for the local (topical) treatment of disorders confined to the mucosa, in both tissue and enterocyte levels.

The disease or disorder is now specified as "a disease or disorder associated with inflammation of the gastrointestinal mucosa." Support for this amendment is found, for example, on page 14 of the description, lines 20-21. See also claims 13, 26, 39 and 58 as originally filed.

The fact that the active ingredient is not covalently bound with the lipid assemblies has been made explicit in claim 62. Support is found on page 7, lines 19-21, of the description.

Claims 62-75 have been rejected under 35 USC 112, first paragraph, for lack of enablement. The examiner states that while the disclosure is enabling for the treatment of inflammation, it does not reasonably provide enablement for treatment or prevention of diseases or disorders of the mucosa.

The claims have been limited to the treatment of a disease or disorder associated with inflammation of the gastrointestinal mucosa. Accordingly, all of the claims are

now directed to the embodiment that the examiner agrees is supported by an enabling disclosure. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 62-75 have been rejected under 35 USC 112, second paragraph, as being indefinite. The examiner says that "active ingredient" and "disease or disorder of the mucosa" in claim 62 are unclear. The examiner notes that claim 69 recites that examples of such disease or disorder include nausea and reflux and it is unclear how these are mucosal diseases or conditions.

With respect to this part of the rejection, the "active ingredient" has now been defined as one that is effective for the topical treatment of said GI mucosa. As to "disease or disorder of the mucosa," claim 62 has been amended to specify that the subject being treated is one "having a disease or disorder associated with inflammation of the GI mucosa." This clarifies the terms that the examiner considered to be indefinite and should obviate this part of the rejection.

The examiner questions what is being conveyed by "Mesalamine (5ASA)" and "Probiotics g. cyclosporin A" in claim 72.

Claim 72 has now been amended to correct clerical and typographical errors therein, this obviating this part of the rejection.

The examiner questions the metes and bounds of "derivatives of 5-aminosalicylic acid."

As to the objection to derivatives of 5-aminosalicylic acid, it is noted that such derivatives for use to treat inflammation of the gastrointestinal mucosa were well known in the art at the time of filing of the application. Submitted herewith is an exemplary reference discussing the use of 5-SAS drugs/derivatives with respect to GI inflammatory conditions. It is Travis, "Which 5-ASA?" *Gut* 51:548-549 (2002). It is clear that this is a term well known to those of ordinary skill in the art and its use does not make the metes and bounds of the claim unclear.

The examiner has noted a typographical error in claim 68, but this has been made moot by the cancellation of this claim.

The examiner states that the metes and bounds of "SOD mimics" and "therapeutic reducing agents" in claim 74 are unclear.

As to the objection to the term SOD mimics, submitted herewith is an exemplary abstract showing that this term would have been well understood by those versed in

the art at the time of filing the application. It is Henke, "Superoxide dismutase mimics as future therapeutics," Expert Opinion on Therapeutic Patents, 9:169-180 (1999). The term "therapeutic reducing agent" is also a term well known to those of ordinary skill in the art and is thus not objectionable. It is well known that a "reducing agent" is a substance that chemically reduces other substances, especially by donating an electron or electrons. Those that can be used therapeutically are covered by this claim.

The examiner states that claim 74 recites the broad recitation of free radical scavengers and also recites tocopherol, SOD, etc., which are narrower statements of the limitation.

Original Claim 74 has been split into two claims (now claims 74 and 80). Accordingly, this part of the rejection has now been obviated.

Accordingly, it is urged that all of the present claims particularly point out and distinctly claim the invention. Reconsideration and withdrawal of this rejection are respectfully urged.

Claims 62-66 and 68-75 have been rejected as being anticipated by Qi (US2003/0095999, now US6,872,406) and argues that Qi teaches anionic liposome delivery of active agents "within the mucosa of the host [for] treatment and

prevention of conditions such as inflammation, nausea …". This rejection is respectfully traversed.

Qi describes fusogenic liposomes carrying on their surface a protein with positively charged amino acids. The term "fusogenic protein or polypeptide" is defined in Qi at pagagraph [0061]. Specifically, the protein is saposin C. In this respect, the following facts should be taken into consideration.

The liposomes of Qi, being fusogenic, deliver the active ingredient via membrane fusion. In fact, Qi emphasizes transdermal delivery for systemic absorption. See paragraph [0130] of Qi ("Transdermal administration typically involves the delivery of a pharmaceutical agent for percutaneous passage of the drug into the systemic circulation of the patient." [Emphasis added]) and the claims of Qi, which clearly define that the delivery of the agent is "through the membrane." See also paragraph [0003] ("the present invention relates to methods for enhancing the transport and delivery of pharmaceutical agents across and/or within dermal and mucosal membranes") and paragraph [0070] ("the terms 'transport' and 'delivery' refers to the passage of a substance across or through the skin (i.e., transdermal), including the epidermis and dermis, or across a mucosal membrane, where the substance can contact, and be

absorbed by the cells of that particular membrane."). Thus, Qi does not describe and even may be regarded as teaching away from topical (local) treatment, as is required by the present claims.

Furthermore, saposin includes positively charged amino acids that are required for its association to the negatively charged phospholiposome membrane (see paragraphs [0090], [0091] and [0174] of Qi). Thus, one would expect that the fusogenic liposome is more zwitterionic than anionic. The present claims require that the lipid assemblies loaded with an active ingredient be negatively charged.

While Qi refers to a variety of drugs that can be carried by the liposome, including anti-inflammatory drugs, there is no true example showing a therapeutic effect of the composition, all the more, an anti-inflammatory effect. All examples concentrate on the formation of the fusogenic liposomes.

Accordingly, none of the present claims are anticipated by the disclosure of Qi. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 62-65 and 68-75 have been rejected as being obvious in view of Qi. The examiner states that it would

have been obvious to prepare compositions for the treatment of various diseases in view of the suggestions of active agent provided in Qi. This rejection is respectfully traversed.

The present invention is directed to the treatment of a disease or disorder associated with inflammation of the gastrointestinal mucosa using negatively charged liposomes loaded with an active ingredient. As detailed above, Qi describes fusogenic liposomes carrying on their surface saposin C, a protein with positively charged amino acids for the purpose of transdermal delivery for systemic absorption. Saposin C includes positively charged amino acids that are required for its association to the negatively charged phospholiposome membrane. Therefore, it is reasonable to assume that the association with the liposome reduces the net negative charge of the entire construct.

Against this, the present invention aims at providing negatively charged liposomes for targeting active agents to disease GI mucosa. Specifically, it has been surprisingly found by the inventors that there is a difference in the absorbance of charged liposomes between healthy and diseased subjects, the negatively charged liposomes adhering to inflamed mucosa while positively charged liposomes adhere to healthy mucosa. This is

evident, at least from the following paragraphs of the present specification:

> Surprisingly, differences in the attachment properties of charged lipid assemblies, such as liposomes, were found, when examined in healthy or inflamed mucosal tissues of rat colon. Specifically, positively-charged liposomes adhered to a healthy mucosa significantly better than anionic or neutral liposomes. [page 13, lines 15-20];
>
> When the attachment of the various types of liposomes was measured in inflamed and healthy tissues, it was found that anionic liposomes adhered better to the inflamed colon than did cationic liposomes (17.8±0.95, 8.5±1.35, 7.05±0.25% fluorescence of initial amount per g tissue wet weight ± SEM for liposomes containing DSPG, DODAB and HSPC, respectively) (Figure 5A). [page 40, lines 5-10];
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> The attraction between the inflamed epithelium and negatively charged groups was verified by the studies involving charged dyes. Figure 6A shows that the anionic dye eosin B adhered significantly better to the inflamed colonic epithelium than to the healthy tissue (0.12±0.011 and 0.19±0.012 $\mu g/cm^2$ for healthy and inflamed tissues, respectively). The cationic dye hematoxylin, on the other hand, adhered significantly better to healthy tissues than to inflamed ones (Figure 6B) (26.2±2.8 and 19.6±1.36 $\mu g/cm^2$ for healthy and inflamed tissues, respectively). [page 40, lines 17-24].

Qi does not teach the specificity of negatively charged liposomes to inflamed mucosa and the unexpected benefits of

such negatively charged liposomes in providing local and inflammation-targeted treatment of conditions within the GI tract. Accordingly, no prima facie case of obviousness has been established and, even if so established, would be rebutted by the unexpected advantages of the present invention. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claim 67 has been rejected as being unpatentable over Qi in combination with Iga, Fossheim, Dyvik or Schneider, individually or in combination. The examiner states that, while Qi does not teach the use of phosphatidylglycerol or a saturated form of phosphatidylglycerol, the secondary references each teach that either phosphatidylserine or phosphatidylglycerol could be used for the preparation of liposomes. This rejection is respectfully traversed.

None of Iga, Fossheim, Dyvik or Schneider supply the deficiencies of Qi discussed above or make obvious the unexpected properties of the use of negatively charged loaded liposome assemblies for treatment of the GI mucosa. Accordingly, claim 67 is allowable for the same reasons as the claim from which it depends.

It is submitted that all of the claims now present in the case clearly define over the references of record and

fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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